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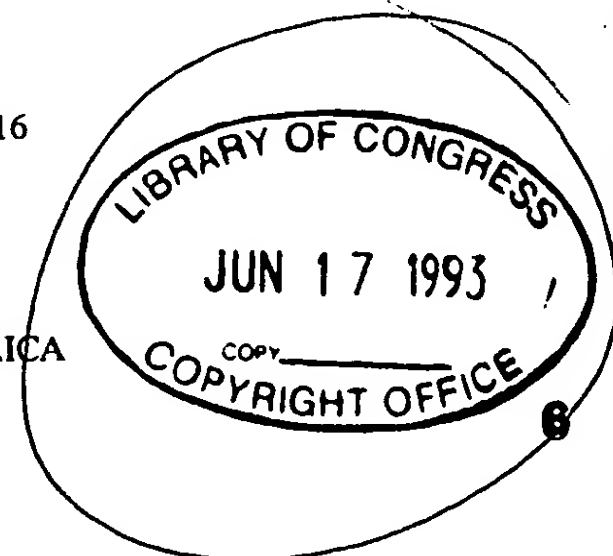
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Synergistic Effects in Percutaneous Enhancement

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I. INTRODUCTION

To use skin as an alternative route for drug administration, the drugs must be potent and have suitable physicochemical properties for efficient transdermal permeation to achieve therapeutic levels in the body. However, most drugs have suboptimal characteristics in this respect, and attempts to achieve full control of percutaneous absorption give rise to major problems, not only because of the relative impermeability of human skin, but also because of its considerably large biological variability.

One approach to render the skin more permeable is to administer a permeation enhancer along with the drug (for review, see 1-4). In the most simple form, the drug can be dissolved or dispersed in a solvent known to decrease the barrier function of the stratum corneum; for example dimethyl sulfoxide, ethanol, propylene glycol, and ethyl acetate, among others, have been used in this way. Another attempt is to use more lipophilic compounds, such as laurocapram (Azone) and derivatives thereof, long-chain alcohols, fatty acids and esters thereof, which probably penetrate the stratum corneum more slowly, but may have a more prolonged effect on the skin barrier resistance. However, it is most efficient to combine a simple solvent with a lipophilic component that by joint work delivers the drug at a requisite rate and degree into the skin.

A mixture of two or more solvents may affect the transport of a drug through the skin in different ways. Basically, the effects can be categorized as follows:

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(a) change in the thermodynamic activity (e.g., by increasing the degree of saturation in the vehicle and, hence, increasing the escaping tendency); (b) specific interaction with the stratum corneum, either by increasing the drug solubility in the stratum corneum (i.e., facilitate partitioning of drug from the vehicle into the skin) or by altering the various pathways (i.e., the polar and nonpolar pathways) of the stratum corneum.

It can be difficult to distinguish between the possible modes of action, and several may be active at the same time. Different experimental setups have been employed to identify the distinction between drug-vehicle interactions and vehicle-skin interactions. These comprise (a) the use of saturated solutions of drugs to maximize the thermodynamic activity, (b) the use of pretreatment of the skin with the enhancer formulation before application of the drug, and (c) the use of skin membranes derived from the stratum corneum. Examples of these methods will be given in the following.

The purpose of this review is to excerpt from the literature examples in which two or more permeation enhancers in mixture have been shown to act synergistically in percutaneous enhancement. A true synergistic effect is achieved when the combination of penetration enhancer elicits a greater effect than the individual components used alone. However, for practical reasons the definition is expanded to comprise all examples for which two or more permeation enhancers in a mixture have worked well together in increasing the transport of drugs into and through the skin.

II. PENETRATION ENHANCERS NOT INCLUDED IN THIS CHAPTER

Several compounds will be discussed in detail in the individual chapters elsewhere in this volume; therefore, they will not be commented on in the present chapter. The compounds include: Azone and derivatives thereof, alkyl esters, surfactants, terpenes, phospholipids, dimethyl sulfoxide and derivatives thereof.

III. PROPYLENE GLYCOL AS A VEHICLE

Propylene glycol (PG) is a commonly used solvent in topical formulations and an efficacious cosolvent for other penetration enhancers (e.g., Azone, polar lipids, and terpenes; 5-9). Thus, it is appropriate to sum up the current knowledge about PG's mode of action in skin penetration enhancement.

Propylene glycol fulfills several requirements for an ideal penetration enhancer; it is nonvolatile, has good solvent properties for many hydrophilic as well as lipophilic drugs, and it has a transient enhancing effect on skin permeation under suitable conditions. It has become an appropriate vehicle for a great variety of

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drugs, for example, glucocorticoids (10), estradiol (11-15), metronidazole (5,14,15), and fluorouracil (12). The effect of PG as a penetration enhancer has been the subject of many discussions in the literature. It is well recognized that PG easily permeates both human skin (5,13,15) and rat skin (16). This observation led Kondo et al. to suggest that the enhancing effect of PG is caused by the constant change of the actual formulation, leading to a higher thermodynamic activity in the vehicle because of the disappearance of PG (16).

However, Barry et al. have shown that pretreatment of skin membranes with PG *in vitro*, 12 hr before application of a solvent-deposited dry drug film, increases the skin permeability of estradiol and fluorouracil, compared with the untreated skin. This must be the result of a direct effect of PG on the skin barrier function, probably owing to an increased drug solubility in the skin or an interaction with proteins of the stratum corneum, as verified by differential scanning calorimetry (DSC) (12,17). In another pretreatment study, PG did not increase the skin permeation, probably because of a prolonged time lag (i.e., 48 hr) between application of PG and the drug, estradiol (13).

Over the years, there has been some confusion about the effect of PG as a penetration enhancer. Thus, PG has alternately been called both an effective and an ineffective solvent used in the neat state. This discrepancy may be mainly due to differences in the research conditions. Consequently, in several instances, it has been observed that the effect of PG is most evident when the horny layer is not fully hydrated (i.e., under nonoccluded conditions; 10-12).

The effect of PG is highly influenced by other vehicle constituents. Therefore, addition of another glycol (e.g., glycerol) effectively reduced the effect of PG, whereas the permeation of estradiol was markedly enhanced by the addition of either hexadecanol or octadecanol (15). However, PG works very well with many components, and examples of these enhancer systems will be given in the following sections.

IV. FATTY ACIDS OR ALCOHOLS IN THE VEHICLE

Two-component systems, consisting of a hydrophilic solvent, such as propylene glycol, and a lipophilic molecule, such as fatty acids or alcohols, are very effective permeation enhancer systems for many drugs, including estradiol (12,18,22,28), progesterone (19), salicylic acid (6,20), acyclovir (7,21,22), narcotic analgesics (23), naloxone (24,25), hydrocortisone (19,22,26), 6-mercaptopurine (27), fluorouracil (12,18), triamcinolone acetonide (28), trifluorothymidine (22,28), nitroglycerin (22,29), retinoic acid (22), indomethacin (30,31), and metronidazole (8). Thus, these enhancer systems are well studied, and their ability to enhance permeation of both polar and nonpolar compounds is obvious.

However, the enhancing effect seems to be most pronounced for the more polar drugs. For example, addition of 2% oleic acid to propylene glycol had no effect on the permeability coefficient of estradiol, compared with propylene glycol in the neat state, whereas the same vehicle increased the permeability coefficient of acyclovir, a very polar compound, by a factor of about 140 (Table 1). On the other hand, by increasing the percentage of oleic acid in the vehicle by 10%, the permeability coefficient of 17 β -estradiol was increased by a factor of 6 (22). Correspondingly, addition of either 5% oleic acid or 5% linoleic acid in propylene glycol had no effect on the permeation of another lipophilic compound (e.g., lidocaine; 21).

From the results in Table 1, it also appears that a choline ester (e.g., lauroylcholine) acts synergistically with oleic acid. The effect of the ternary mixture of oleic acid, lauroylcholine, and propylene glycol on the permeation of both estradiol and acyclovir was much greater than the sum of the corresponding binary mixtures (e.g., oleic acid or lauroylcholine in propylene glycol; 22).

Metronidazole is a drug with intermediate polarity and, therefore, is susceptible to polar lipid-propylene glycol vehicles (8). Figure 1 illustrates the transport rate of metronidazole from vehicles containing an increasing percentage of polar lipids up to 10% in the PG vehicles. The results show that all of three polar lipids—linoleic acid, oleic acid, and oleyl alcohol—produce an enhanced drug permeation. [Direct comparisons are not possible because of varying permeation hours.] Addition of only a small amount of oleyl alcohol to the PG vehicle provides a rather large increase in the metronidazole transport. As the concentration of oleic acid or linoleic acid is increased, the drug transport is also increased, up to a point.

Table 1 Effect of Oleic Acid (OA) and Lauroylcholine Iodide (LCI) on the Permeability of 17 β -Estradiol and Acyclovir Through Hairless Mouse Skin In Vitro From Saturated Solutions in Propylene Glycol (PG) Vehicles^a

Vehicle	17 β -Estradiol		Acyclovir	
	C_d^a (mg/mL)	P/P_{PG}^b	C_d (mg/mL)	P/P_{PG}^b
PG	101	1.0	8.13	1.0
PG + 2% v/v OA	123	1.3	4.93	138.6
PG + 2% w/v LCI	95	6.9	5.29	ND ^c
PG + 2% v/v OA + 2% w/v LCI	128	14	5.08	404.5

^a C_d is the solubility of drug in the vehicle at 35°C and P is the permeability coefficient.

^b P_{PG} (17 β -estradiol) = 4.91×10^{-6} cm/hr; P_{PG} (acyclovir) = 2.02×10^{-5} cm/hr.

^cNot detectable.

Source: Ref. 22.

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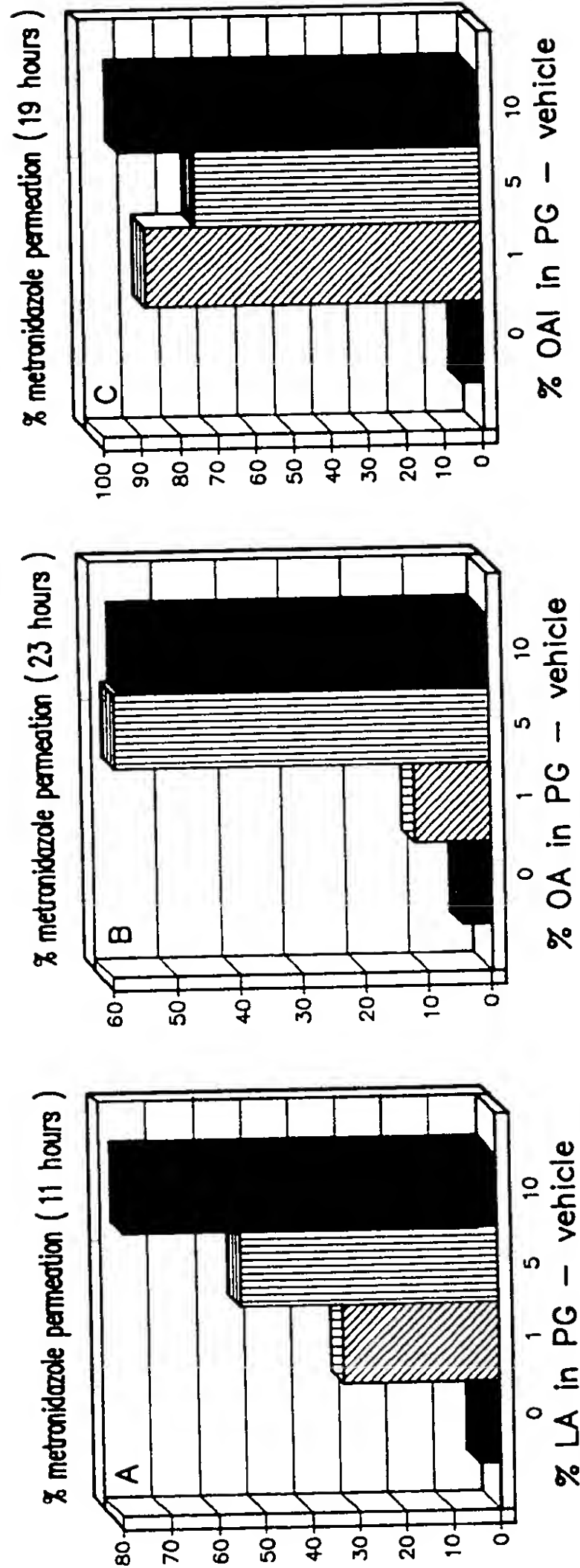


Figure 1 Effect of addition of polar lipids on the permeation of metronidazole in propylene glycol vehicle across human skin in vitro. LA, linoleic acid; OA, oleic acid; OAI, oleyl alcohol. (From Ref. 8)

For example, PG with 10% linoleic acid, gives a 30-fold increase in the transport rate (see Fig. 1).

Most of the studies on fatty acid penetration enhancers have focused on oleic acid, and to a lesser extent, linoleic acid. Both oleic acid and linoleic acid are unsaturated fatty acids with a *cis*-configuration. Accordingly, it has been proposed that the effects of these compounds are associated with the linked structure owing to the *cis* double bond (3,6,20). The enhancement effect of a series of octadecenoic acids was assessed by measuring the flux of salicylic acid through porcine stratum corneum. It was found that a greater flux is achieved with the *cis*- than with the corresponding *trans*-isomer, and that the enhancing effect increased with increasing distance of the *cis* double bond from the carboxylic group (20).

However, in a profound study on the structure-effect relation of fatty acid isomers, Aungst and coworkers found that the corresponding *trans*-isomers to oleic acid, elaidic acid, and to linoleic acid, linolelaidic acid, had substantially the same effect on the skin penetration of naloxone as the *cis*-isomers. Furthermore, they found that saturated acids, also, but to a much lesser extent, enhance the penetration rate, with an optimum at C₉-C₁₂ chain length, for which the flux of naloxone was increased 20- to 40-fold. Branched saturated fatty acids were superior to unbranched compounds in only one case. Thus, isostearic acid (C₁₈), branched at a position distant from the carboxylic acid group, was significantly more effective in enhancing the naloxone flux than was the stearic acid. However, this was not true for the isostearic acid branched in a position proximal to the carboxylic acid group. This indicates the possibility that some branched fatty acid isomers may have an effect on skin permeation different from unbranched isomers, depending on the position or chain length of the branch (24,25).

Diols other than propylene glycol have been used in mixtures with oleic acid; for example, 1,2-butanediol and 1,2-hexanediol. But, although an effect of the mixed system on salicylic acid permeation compared with the solvent used alone was observed, the enhancing ability was much less than for propylene glycol as the base solvent (6). Correspondingly, oleic acid gave far less enhancement of the permeation of 17 β -estradiol, triamcinolone acetonide, and trifluorothymidine, when propylene glycol was replaced by 2-ethyl-1,3-hexanediol (28).

It is now well accepted that the mechanism by which fatty acids in mixtures with, for example, propylene glycol increase the skin permeability involves an interaction with the intercellular lipids in the stratum corneum. Alteration of the lipid bilayers has been assessed using differential scanning calorimetry (DSC) and Fourier transformation infrared spectroscopy (FTIR) (3,17,20,32,33). These methods indicate that the enhancer system causes a disruption of the ordered lamellar structure of the bilayers in the stratum corneum, leading to an increased fluidization of the intercellular medium. It is likely that propylene glycol enhances the oleic acid penetration, and oleic acid promotes the propylene

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glycol permeation. This mutual effect could thus result in a more rapid diffusion of the drug molecules across the skin.

V. ESTERS OF FATTY ACIDS OR ALCOHOLS IN THE VEHICLE

Isopropyl myristate (IPM) is a commonly used oily liquid in topical preparations, and mixtures of IPM and PG have been effective vehicles for some drugs (e.g., nicorandil and nicardipine; 34,35).

In a comprehensive study on nicorandil permeation across hairless rat skin, Sato et al. (34) examined the effects of a series of binary mixtures of IPM and PG. Figure 2a shows the relationship between the IPM content and the pseudo-steady state flux. The flux was markedly increased by addition of 1% IPM, compared with that of the neat PG vehicle, and was kept approximately constant up to 50% IPM. However, to maximize thermodynamic activity, the drug was applied in saturated solutions. The solubility of nicorandil varied with the IPM content and, to compensate for this, the permeability coefficient can be estimated (i.e., the flux divided by the drug solubility in the vehicle). Figure 2b shows the approximate relation between the IPM content and the permeability coefficient of nicorandil. The results clearly demonstrate the paradox of using either flux or the permeability coefficient to evaluate the vehicle effect. Thus, from the permeability coefficient relationship, 10% IPM-PG seems to be equivalent to neat IPM. However, from the flux relationship, it is obvious that the 10% IPM-PG delivers 20–30 times more nicorandil through the skin per hour than neat IPM. The difference between the 10% IPM-PG vehicle and the neat PG vehicle, as seen with full-thickness skin, vanished when the skin was deprived of the stratum corneum by stripping. Therefore, it was suggested that IPM had a direct effect on the stratum corneum. The influence of different isopropyl esters, with varying chain length (C₃, C₅, C₇, C₁₃, and C₁₅) on nicorandil permeation was also investigated in mixtures with PG. Isopropyl myristate showed an intermediate effect, whereas isopropyl butyrate and isopropyl hexanoate were twice as effective.

In another study with adenosine, IPM in mixtures with propionic acid was used as a vehicle. The permeability coefficient of adenosine was increased with increasing content of IPM. Thus, the permeability coefficient of adenosine was increased fivefold by addition of 25% IPM, compared with neat propionic acid (36).

Several homologues of midrange *n*-alkyl fatty acid esters in a mixture with alcohol have been evaluated as potential enhancers of skin permeability. In the series, ranging from C₆ through C₁₂, optimal enhancement of minoxidil transport across hamster skin occurred with the methyl nonanoate (C₉) and methyl caprate (C₁₀). Thus methyl caprate produced a sevenfold increase in the amount of minoxidil absorbed, compared with neat alcohol as a vehicle, and the methyl

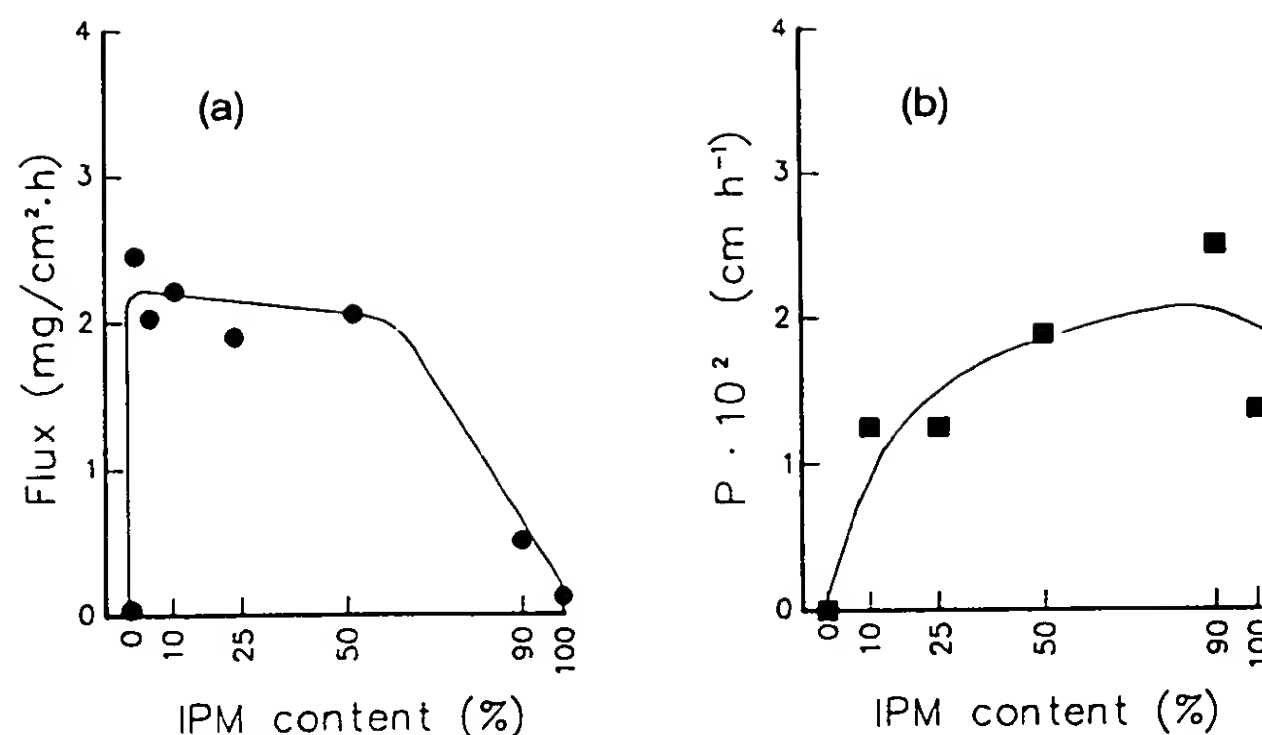


Figure 2 Effect of isopropyl myristate content in isopropyl myristate-propylene glycol vehicles on the permeation rate of nicorandil (a) and permeability coefficient of nicorandil (b) in hairless rat skin. (Data from Ref. 34)

esters were more effective than the corresponding ethyl and propyl esters (37). Besides minoxidil, methyl caprate enhanced the skin permeability of $1\alpha,25$ -dihydroxycholecalciferol, erythromycin, hydrocortisone, triamcinolone acetate, and testosterone. At a fixed concentration of 10% in alcohol, methyl caprate produced a 7-, 21-, 8-, 5-, and 13-fold increase, respectively, in skin penetration of the drug through hamster ear skin (37).

To elucidate the enhancing effects of fatty alcohol-lactic acid esters, cetyl lactate was selected as a candidate to increase the percutaneous absorption of indomethacin through rat skin in vivo. Addition of 3% cetyl lactate to propylene glycol greatly increased the bioavailability of indomethacin by a factor of 170. It was suggested that cetyl lactate had a direct effect on the barrier function of the stratum corneum, as the PG vehicle without cetyl lactate and the PG vehicle with cetyl lactate yielded the same percutaneous absorption of indomethacin through skin from which the stratum corneum had been stripped (38).

VI. PYRROLIDONES AND UREAS IN THE VEHICLE

Many compounds identified as components of the natural moisturizing factor of stratum corneum have been evaluated as potential penetration enhancers. Most

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promising results have been obtained by using naturally occurring fatty acids or analogues thereof, as previously mentioned, but also pyrrolidones and urea have been investigated to some extent. The most widely studied derivatives of the naturally occurring pyrrolidone carboxylic acid are 2-pyrrolidone and *N*-methylpyrrolidone (NMP), which have been effective in enhancing the permeation of, among others, hydrocortisone; a polar model compound, mannitol (19); and indomethacin (39).

The effect of including 5% NMP in a hydrophilic vehicle, propylene glycol, and a lipophilic vehicle, isopropyl myristate, on metronidazole permeation has been investigated using full-thickness human skin in vitro. It appeared that the delivery of metronidazole was not unaffected by including NMP in propylene glycol, whereas NMP alone and in a mixture with isopropyl myristate promoted the drug permeation three- to fourfold, compared with neat propylene glycol. The marked difference in drug permeation from vehicles based on propylene glycol and isopropyl myristate cannot be due to differences in the thermodynamic activity in the vehicles, as the drug solubility in the vehicles is almost similar (Table 2). The permeation of metronidazole is linearly correlated with the permeation of the enhancer itself, NMP; therefore, it is assumed that the degree of NMP permeation plays a predominant role in drug transport through the skin (Fig. 3; 8).

The skin permeability of very large molecules, such as insulin, is extremely low, but improved permeation by means of penetration enhancer systems has been reported (40,41). Thus, in vitro transdermal absorption of insulin was improved when NMP was incorporated in aqueous PG through pig skin and rat skin vehicles. The maximum penetration efficacy depended on optimal concentrations of both NMP and propylene glycol. *N*-Methylpyrrolidone showed maximum efficacy at a concentration of about 10%, and the optimum concentration of PG was 40%. The use of the vehicle alone or of the penetration enhancer without the vehicle resulted in very low efficiency, whereas the combination of the vehicle and the penetration enhancer resulted in a pronounced effect (40,41).

Table 2 Comparison of 23 hr Permeation of Metronidazole From Various Vehicles Across Human Skin In Vitro

Vehicle	Enhancement ratio	Solubility of metronidazole (mg·g ⁻¹)
A (PG)	1.0	18
B (NMP)	2.7	187
C (NMP/PG)	0.95	22
D (NMP/IPM)	3.8	25

Source: Ref. 8

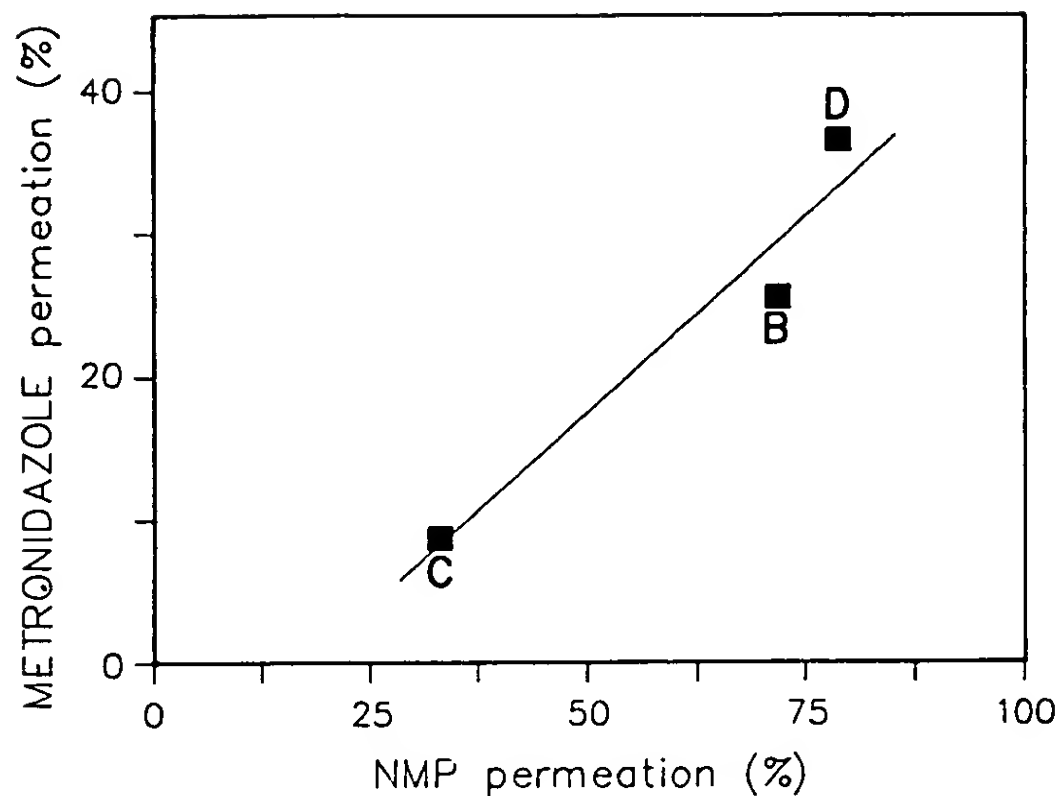


Figure 3 Comparison of a 23 hr permeation across human skin in vitro of metronidazole and *N*-methylpyrrolidone in percentage of amount applied from various vehicles. B, neat *N*-methylpyrrolidone vehicle; C, *N*-methylpyrrolidone-propylene glycol vehicle; D, *N*-methylpyrrolidone-isopropyl myristate vehicle. (Data from Ref. 8)

Well-known penetration enhancers, such as Azone and decylmethyl sulfoxide, contain a medium-length hydrocarbon chain of C_{12} and C_{10} , respectively. Therefore, with the purpose of simulating their effect on the skin permeability, urea derivatives containing one or two similar alkyl groups, 1-dodecylurea and 1,3-didodecylurea, together with a derivative with two aryl groups, 1,3-diphenylurea, were synthesized (42). In Figure 4 the activity of the urea analogues is clearly demonstrated in terms of the enhancement ratios; that is, the ratio between the permeability coefficient of fluorouracil before and after application of the penetration enhancer system. The vehicles alone (i.e., liquid paraffin, dimethylisorbide, and propylene glycol) and urea saturated in the vehicles produce no significant increase in the permeability coefficient of fluorouracil. Also no significant difference exists in the penetration activities of the three urea analogues in a given vehicle. However, the choice of a cosolvent for the urea analogues clearly affects the efficacy. In particular, when applied as a saturated solution in propylene glycol, the enhancement ratios of the urea derivatives are significantly greater than when applied saturated in dimethylisorbide or liquid paraffin (42).

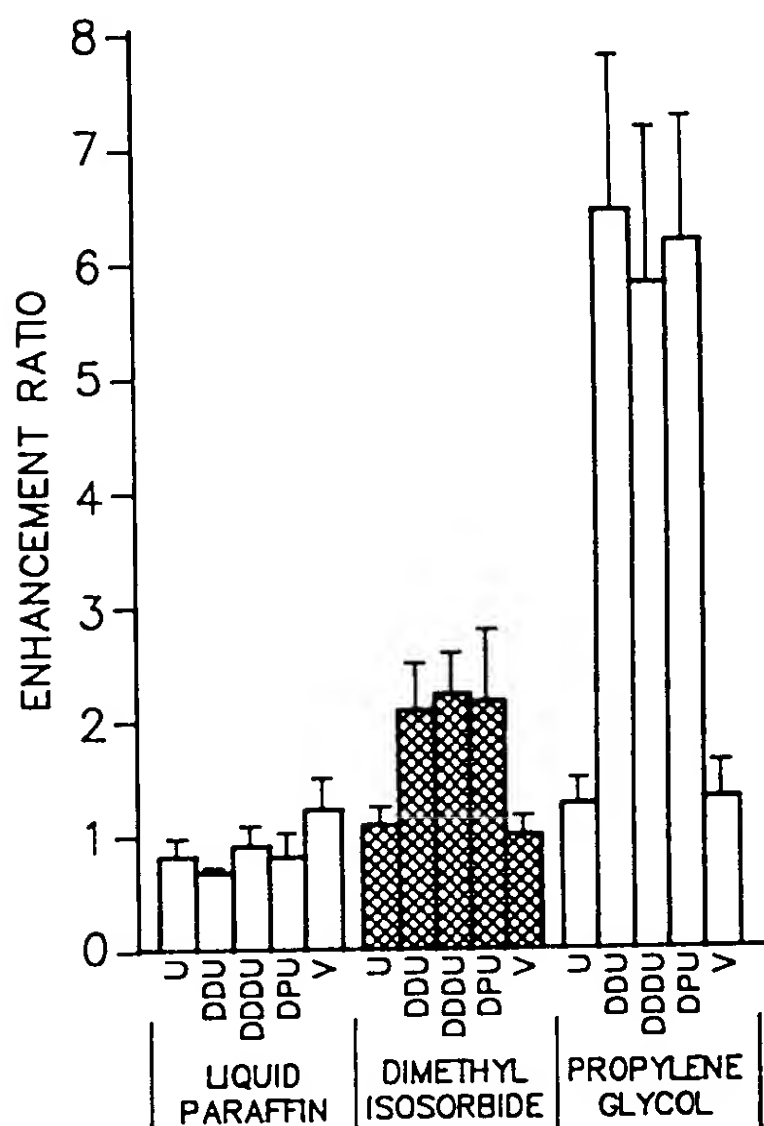


Figure 4 The mean enhancement ratios of urea and the analogues from the three vehicles on fluorouracil permeation across human epidermal membranes. U, urea; DDU, 1-dodecylurea; DDDU, 1,3-didodecylurea; DPU, 1,3-diphenylurea; V, vehicle alone. (From Ref. 42)

VII. CONCLUSION

Many compounds act as penetration enhancers because of their ability to pass into the skin and, in so doing, reversibly decrease its resistance to drug passage. The range of enhancers discovered so far indicates that many commonplace substances in the pharmaceutical or cosmetic industries might be effective. Propylene glycol, a solvent widely used in topical formulations, is highly effective as a cosolvent for many potent penetration enhancers. However, propylene glycol is not generally applicable as a cosolvent. For example, *N*-methylpyrrolidone is active only in very high concentrations in propylene glycol, whereas lower concentrations are needed in isopropyl myristate. The use of penetration enhancers in high concentrations will increase the risk of dermal toxicity.

In the past, the risks of irritative or contact allergic effects of penetration enhancers have received only little attention, and it has been more or less implied that local toxicological effects are inseparably linked to the effect as a penetration enhancer. However, in a structure-effect study of fatty acid isomers in propylene glycol vehicles, no distinct correlation between the naloxone skin penetration enhancement and the irritation potential of the vehicles was found. The importance of this is that some penetration enhancers can increase the skin permeability, but not at the expense of causing irritation (25).

Another area that is receiving growing attention is the possible biotransformation of drugs and other compounds during their passage through the skin. Current knowledge about the metabolizing capacity of skin has been exploited to increase the bioavailability of drugs by designing prodrugs that, after diffusion into and through the skin, undergo enzymatic reconversion into the parent active drug molecules. Another approach to increase the bioavailability of drugs that are subject to degradation in the skin would be to administer a compound along with the drug that inhibits the enzyme activity. The possible interaction between the penetration enhancers and the enzyme systems of skin await future investigation.

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PENETRATION ENHANCERS IN SKIN PERMEATION

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INTRODUCTION

In recent years, the problems involved in controlling drug input into human skin have been brought into sharp focus by the efforts of pharmaceutical firms to develop transdermal delivery devices, such as those used to supply scopolamine, nitroglycerin, estradiol, and clonidine (marketed patches), or testosterone and fentanyl (under development). Except for scopolamine, the marketed products have not achieved full flux control, mainly because of the relative impermeability of human skin and its biological variability, site to site and centimetre by centimetre (Scheuplein, 1978; Schaefer et al, 1982; Bronaugh and Maibach, 1985; Barry, 1983). Essentially, for such control to operate, we require that the stratum corneum should behave as if it were a perfect sink and thus swiftly remove molecules as they partition from the device, rapidly delivering them to the viable skin tissues for further transport to the systemic circulation. To achieve this for molecules in general and drugs in particular, one approach would be to remove the horny layer by, for example, stripping it with sticky tape - a procedure doomed to gain the manufacturer few friends among the patient population! Alternatively and more reasonably, we could include suitable penetration enhancers in the formulation. These are molecules designed to display the sole property that they reversibly remove the barrier resistance of the stratum corneum and so permit the unhindered access of the drug to the viable tissues.

The remainder of this presentation will consider aspects of our work (some new, some published) which have been directed at elucidating the mechanisms of action of a variety of penetration enhancers. We have been interested in these molecules in the light of their possible general utility, but most especially in regard to transdermal delivery devices and the peptide drugs of tomorrow. Our experimental enhancers include Azone, 2-pyrrolidone, N-methylpyrrolidone, dimethylsulfoxide, dimethylformamide, dimethylacetamide, N-methylformamide, decylmethylsulfoxide, leic acid and propylene glycol.

DIFFERENTIAL SCANNING CALORIMETRY

When human stratum corneum samples are hydrated, hermetically sealed in pans and scanned in a differential scanning calorimeter, a characteristic 4-peak trace, representing the endotherms, usually develops. These endotherms typically occur at 38°C (T1), 72°C (T2), 85°C (T3), and 102°C (T4), results similar to those found by Van Duzee (1975). Endotherms T1 to T3 arise mainly from lipid melting, whereas T4 is because of protein denaturation. Azone removes the first three peaks, and therefore appears to work as an enhancer by disrupting horny layer lipid structure. Oleic acid acts similarly. Decylmethylsulfoxide lowers T2 and T3, but does not alter their areas, and it affects the protein -T4 falls (Goodman and Barry, 1985, 1986a, b).

PERMEATION STUDIES - Cadaver Skin

When examining the mode of action of enhancers, it is valuable to select a range of penetrants of different polarities so as to decide if a potential enhancer modifies mainly the polar route through the skin, the lipid route or both pathways together. In one program of work, we selected mannitol as a polar material, progesterone as a lipid penetrant, and hydrocortisone as a diffusant with intermediate characteristics. We assessed by how much various enhancers promoted their penetration through human skin under an in vivo mimic experimental design.

We can summarise the main effects of the enhancers we examined as showing that the accelerants fell into three main categories:

- a) Enhancers which promote permeation through both polar and lipid routes i.e. propylene glycol plus Azone, 2-pyrrolidone, N-methylpyrrolidone, and N-methylformamide.
- b) Accelerants which preferentially affect the polar pathway, such as propylene glycol plus decylmethylsulfoxide.
- c) Penetration enhancers which mainly modify the lipid route e.g. propylene glycol and propylene glycol plus oleic acid.

The importance of the correct choice of cosolvent was confirmed, particularly for materials such as Azone and cis-unsaturated oleic acid.

PERMEATION STUDIES - Cadaver Skin Versus Hairless Mouse Skin

In recent years, hairless mouse skin has gained a reputation as a good model for human skin. In certain circumstances, this is justified, but we need to be cautious. For example, we found that when we used this tissue to investigate the action of enhancers, it always over-emphasised the accelerant activity compared with human tissue - sometimes markedly so. Thus, in one experiment we compared the effects of Azone, decylmethylsulfoxide, propylene glycol, and oleic acid on the penetration of 5-fluorouracil through both skin types. The technique employed was a steady state design with 12-hour pretreatment of the skins with the test enhancers - normal saline was used as a control. Mixtures of Azone in propylene glycol and oleic acid in propylene glycol increased the drug permeability coefficient through both skins, but the effect in hairless mouse was seven-fold greater than for cadaver membranes!

From these results, and other work of ours with extended hydration and acetone treatments, it appears that hairless mouse skin is particularly susceptible to chemical perturbation. This has obvious implications if the results of mouse studies were to be applied directly to man, without correction.

PERMEATION STUDIES - THE VASOCONSTRICTOR ASSAY.

The human vasoconstrictor assay for topical steroids is an excellent procedure for assessing the factors which modify the bioavailabilities of these drugs, used as such or as model compounds. The test simply scores the degree of pallor induced in the forearms of volunteers.

Using our modification of the occluded vasoconstrictor assay, we assessed the bioavailability of 0.1% betamethasone 17-benzoate in a number of solvents. No attempt was made to adjust the steroid concentration to a constant chemical potential, nor was any allowance made for different partition coefficients (stratum corneum to solvent). At this stage of our work, we were simply looking for dramatic effects. The result was that only N-methylpyrrolidone showed significant enhancing potential (Barry et al, 1984).

This type of procedure has at least two drawbacks - the lack of thermodynamic control and the occluded test procedure. For our second trial, therefore, we kept the chemical potential approximately constant (equivalent to 10% saturation) and we tested the systems under nonoccluded conditions so as to avoid the swamping effect caused by hydrating the stratum corneum. We then saw that 2-pyrrolidone, N-methylpyrrolidone, and Azone or oleic acid plus propylene glycol increased the bioavailability of the steroid (Bennett et al, 1985).

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